

Universidade do Porto, Instituto de Ciências Biomédicas Abel Salazar, Mestrado Integrado em Medicina

## **Clinical significance of ductus venosus waveform as generated by pressure-volume changes in the fetal heart**

Autor: Madalena Peixoto de Sousa Braga  
E-mail: [madalena.braga3@gmail.com](mailto:madalena.braga3@gmail.com)

Orientador: Prof. Doutor Luís Guedes-Martins  
Co-orientador: Dr. Joaquim Gonçalves

**M**  
**2018**



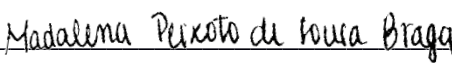
# **Clinical significance of ductus venosus waveform as generated by pressure-volume changes in the fetal heart**

Este trabalho está organizado e formatado de acordo com as regras de publicação da revista “Current Cardiology Reviews”.

URL: <https://benthamscience.com/journals/current-cardiology-reviews/author-guidelines/#top>

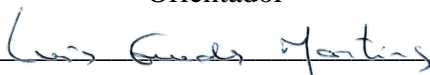
Data de acesso: 1 de Maio de 2018

Autor



(Madalena Peixoto de Sousa Braga)

Orientador



(Prof. Doutor Luís Guedes-Martins)

Co-orientador

  
(Dr. Joaquim Gonçalves)

Maio, 2018

**Agradecimentos:**

Na realização da presente dissertação, contei com o apoio direto ou indireto de múltiplas pessoas. Correndo o risco de injustamente não mencionar algum dos contributos quero deixar desde já expresso os meus agradecimentos ao orientador desta dissertação, o Prof. Doutor Luís Guedes-Martins, pelo apoio, paciência, disponibilidade, transmissão de conhecimentos e interesse por esta área. Ao co-orientador, Dr. Joaquim Gonçalves, pelo seu incentivo, disponibilidade e apoio na elaboração deste trabalho.

## Índice

<i>Abstract.....</i>	<b>2</b>
<i>Keywords.....</i>	<b>2</b>
<i>Introduction.....</i>	<b>3</b>
<i>Methods.....</i>	<b>4</b>
<i>Ductus venosus development and anatomy .....</i>	<b>4</b>
<i>Ductus venosus shunting.....</i>	<b>6</b>
<i>Fetal ductus venosus flow assessment in daily clinical practice .....</i>	<b>9</b>
<i>Ductus venosus Doppler to screening of cardiac defects.....</i>	<b>15</b>
<i>Ductus venosus Doppler contribution to screen for chromosomal defects.....</i>	<b>16</b>
<i>Ductus venosus Doppler in the management of intrauterine growth restriction.....</i>	<b>17</b>
<i>Ductus venosus Doppler contribution to screening of monochorionic twin complications.....</i>	<b>19</b>
<i>Agenesis of the ductus venosus.....</i>	<b>20</b>
<i>Patent ductus venosus .....</i>	<b>22</b>
<i>Conclusion .....</i>	<b>23</b>
<i>List of Abbreviations .....</i>	<b>24</b>
<i>Ethics Committee Approval .....</i>	<b>24</b>
<i>Peer-review .....</i>	<b>24</b>
<i>Author Contributions.....</i>	<b>25</b>
<i>Conflicts of Interest.....</i>	<b>25</b>
<i>Acknowledgements .....</i>	<b>25</b>
<i>Financial Disclosure .....</i>	<b>25</b>
<i>References .....</i>	<b>25</b>

**Title:** Clinical significance of ductus venosus waveform as generated by pressure-volume changes in the fetal heart.

*Authors:*

M. Braga<sup>1</sup>, L. Moleiro<sup>2</sup>, \*L. Guedes-Martins<sup>1,2,3,4</sup>

*Affiliations:*

<sup>1</sup>Instituto de Ciências Biomédicas Abel Salazar, University of Porto, 4050-313 Porto, Portugal

<sup>2</sup>Centro Hospitalar do Porto EPE, Centro Materno Infantil do Norte, Departamento da Mulher e da Medicina Reprodutiva, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal

<sup>3</sup>Unidade de Investigação e Formação – Centro Materno Infantil do Norte, 4099-001 Porto, Portugal

<sup>4</sup>Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-319 Portugal

**\* Corresponding author's e-mail:** luis.guedes.martins@gmail.com (Tel: +351965130529)

**Running head:** Ductus venosus waveform.

**Conflicts of interest:** None declared.

**Manuscript word, table and figure count:** 8799 words and 3 figures.

## **Abstract**

The ductus venosus (DV) is a vascular shunt situated within the fetal liver parenchyma connecting the umbilical vein to the inferior vena cava. This vessel acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the myocardium and brain. Increased impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes. This review serves to improve our understanding of the mechanisms that regulate the blood flow redistribution between the fetal liver circulation and fetal heart and the clinical significance of the DV waveform as generated by pressure-volume changes in the fetal heart.

## **Keywords**

Ductus venosus / fetal venous circulation / ductus venosus shunting / ultrasound / Doppler velocimetry.

## **Introduction**

The ductus venosus (DV) is a vascular shunt situated within the fetal liver parenchyma connecting the umbilical vein (UV) to the inferior vena cava (Figure 1). This vessel acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the brain and myocardium, projecting a high-velocity jet flow posteriorly, from the umbilical vein to the foramen ovale [1]. The blood distribution through the DV is related to changes in umbilical venous pressure, blood viscosity, and an active regulation of the diameter of the entire DV [2]. Anatomically, the DV and the intrahepatic branches of the portal vein are arranged in parallel [3]. During pregnancy, the mean fraction of blood shunted through the ductus is not a constant [2,3]. In human fetuses, the DV shunting rate is approximately 20-30%, and increases in the DV shunting rate are a general adaptational mechanism to fetal distress [3] during extreme challenges of placental compromise or hypoxemia [2,4,5]. Additionally, the DV acts as a transmission line to the umbilical vein from pulse waves generated in the heart [2]. These waves, which may reflect cardiac function, are substantially influenced by the local variation of impedance and compliance [1]. An increased pulsatility index or impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes [6,7-9]. This review serves to improve our understanding of the mechanisms that regulate the blood flow redistribution between the fetal liver circulation and the DV and to analyze the clinical significance of the DV waveform as generated by pressure-volume changes in the fetal heart.

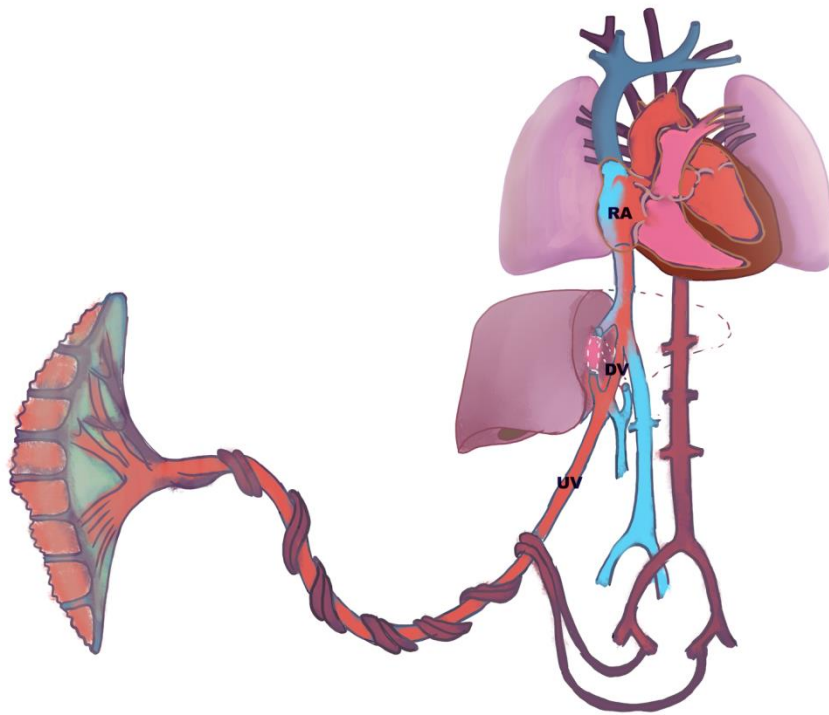


Figure 1. Anatomy of the ductus venosus (DV). The **DV** is a vascular shunt situated within the fetal liver parenchyma connecting the umbilical vein (UV) to the inferior vena cava and right atrium (RA).

## Methods

To compose this review, a thorough literature search was repeatedly performed in PubMed and Medline, with a limitation for articles written in the English language. Search terms used were DV, fetal venous circulation, DV shunting, ultrasound, and Doppler velocimetry.

## Ductus venosus development and anatomy

The arteries and veins are developed by a combination of vasculogenesis and angiogenesis [10]. This process involves a series of steps. Vasculogenesis (VS) is the process of blood vessel formation occurring by de novo production of endothelial



cells and the construction of the primitive vascular plexus inside the embryo. Sometimes VS is treated as synonymous with angiogenesis, which is responsible for the remodeling and expansion of this network. VS is under the control of signaling molecules secreted from endoderm cells and begins first in the yolk sac at day 17, where Indian hedgehog, bone morphogenic protein, and transforming growth factor  $\beta$  (TGF- $\beta$ ) modulate the yolk sac's mesoderm to originate hemangioblastic aggregates [11]. These cellular hemangioblastic aggregates are composed for hematopoietic stem cells and endothelial cells that coalesce to form the extraembryonic umbilical vessels to act as a circulatory connection between the embryo and the maternal compartments. Much of this complex vascular network development is under the influence of vascular endothelial growth factor (VEGF) [10-13]. In addition, angiogenesis remodels this vascular system, promoting vascular intussusception that is facilitated by hypoxia. Oxygen depletion activates the expression of several genes, including those encoding VEGF, angiopoietin-2, and nitric oxide synthase [11]. These proteins are important modulators of cell proliferation induction, guided migration, differentiation and cell-to-cell communication [14].

At 4 weeks of gestation, a group of capillary networks begins to develop into the definitive veins of the embryo. At the same time, three paired venous systems form. The vitelline veins drain the yolk sac and the developing gastrointestinal tract, the umbilical veins return oxygenated blood from the placental tissue, and the cardinal veins drain the embryo [11]. Before the vitelline vein enters the venous end of the heart (sinus venosus), it forms the hepatic sinusoids in the developing liver [11]. The left vitelline vein regresses, and the enlarged right vitelline vein in the liver becomes the DV [10,11]. The umbilical vein brings oxygenated blood from the placenta to the

heart. Initially, the umbilical veins are paired, but as the embryo develops, the right umbilical vein degenerates, whereas the left persists [11]. The left umbilical vein forms a direct anastomosis with the DV, which delivers oxygen- and nutrient-rich blood from the placenta to the embryo-fetal heart. After birth, under normal conditions, the DV regresses and becomes the ligamentum venosum.

### **Ductus venosus shunting**

The mechanism of redistribution of blood flow between the fetal liver and the DV is still a matter of debate [3]. DV shunting corresponds to the percentage of umbilical blood flow that enters the DV, which is arranged in parallel to the intrahepatic branches of the portal vein [3] (Figure 1). This aspect is of particular relevance because the amount of blood that is conducted by the DV is proportional to the resistance of the hepatic venous circulation [15,16]. In other words, the flow regulation in the DV is a variable dependent on the degree of permissiveness to the flow through this blood channel.

DV shunting can be assessed during pregnancy using the indicator dye-dilution method, a radioactively labeled microsphere technique, and blood flow volume measurement using the Doppler ultrasound technique. In experimental situations in which the degree of blood flow through the DV is evaluated, the increase in the DV shunting rate is a defense mechanism. Therefore, theoretically, an increased DV/UV ratio is a sign of a potential hemodynamic compromise. The proportion of umbilical blood shunting through the DV has been evaluated in several animals, such as sheep [17-26], macaques [27], baboons [5-28], marmosets [5] and, finally, humans [15,16,25,29-32].

Approximately 2 decades ago, Bellotti and colleagues [31] used color Doppler sonography to study umbilical, DV, and hepatic flows in 137 normal fetuses between 20 and 38 weeks of gestation. In all of the venous segments examined, blood flow increased significantly with advancing gestational age [31]. The weight-specific amniotic umbilical flow did not change significantly during gestation ( $120 \pm 44$  ml. min<sup>-1</sup> kg<sup>-1</sup>), whereas DV flow decreased significantly (from 60 to 17 ml min<sup>-1</sup> kg<sup>-1</sup>). The percentage of umbilical blood flow shunted through the DV decreased significantly (from 40% to 15%); consequently, the percentage of flow to the liver increased during gestation. The right lobe flow changed from 20 to 45%, whereas the left lobe flow was approximately constant (40%) [31]. The authors suggested that these changes are related to different patterns of growth of the umbilical veins and DV diameters [31], and the findings support the hypothesis that the DV plays a less important role in shunting well-oxygenated blood to the brain and myocardium in late normal pregnancy than in early gestation, which leads to increased fetal liver perfusion [31].

The degree of shunting through the DV in the human fetus seems to be associated with fetal growth. In the study of Kiresud and colleagues, the average fraction shunted through the DV was 28% to 32% at 18 to 20 weeks, decreased to 22% at 25 weeks, and reached 18% at 31 weeks [30]. In this cross-sectional ultrasonographic study, fetuses at <10th percentile for birth weight had significantly more shunting (1.4%) than those at >90th percentile (95% confidence interval, 0.1%-2.7%;  $p=0.04$ ) [30]. In fact, Doppler velocimetry of the DV is abnormal only when fetuses are severely

compromised, whereas the ratio of DV to UV flow rates might be an indicator of impaired fetal condition [33].

Tchirikov and colleagues have analyzed the blood flow rate through the liver as the difference between umbilical venous and DV blood flow [33]. The authors observed that the liver blood flow was significantly decreased in pregnancies with intrauterine growth retardation compared with normal pregnancies [33], and the normalized liver perfusion was significantly decreased only in intrauterine growth retardation pregnancies [33]. The relative increase in DV blood flow in intrauterine growth retardation was attributed by the authors to an increase in hepatic vascular resistance and not to increases in the DV diameter. Later, the same group of authors hypothesized that changes in blood content of the liver evoked alterations to the vascular geometry of the DV, which would also affect its resistance to flow [33]. As a consequence, these results suggest that the main factor responsible for the DV shunting regulation is the degree of resistance achieved by the portal circulation, the latter acting as a functional modulator of the flow through the DV.

Jensen and colleagues have examined the effect of graded reduction in uterine blood flow on distribution of cardiac output and oxygen delivery to fetal organs and venous blood flow patterns in 9 fetal sheep using the radionuclide-labeled microsphere technique [24]. The results of this experiment described a graded reduction in uterine blood flow that induced a redistribution of fetal oxygen delivery and in venous flow patterns [24], influencing the DV shunting. Approximately 15 years later, the umbilical venous flow, DV blood flow, and blood flow to the fetal liver in 56 severely intrauterine growth-restricted fetuses with an abnormal pulsatility index of the umbilical artery were compared with 137 normal control fetuses [16]. In severe

intrauterine growth-restricted fetuses, Doppler examination of blood flow volume showed a significant increase in the shunting of umbilical vein blood flow through the DV and noted a relatively constant blood flow to the heart and brain at the expense of fetal hepatic perfusion [16]. These observations suggested that chronic hypoxia promotes the flow of more oxygenated blood from the DV towards the left heart, coronary circulation and fetal brain, which is a much more ancillary effect to achieve in acute situations or in cases of severe fetal UV compromise. This reasoning can be observed in one experimental study performed in 11 anesthetized pregnant sheep, in which the obliteration of one umbilical artery increases the DV/umbilical vein volume flow (mL/min/kg) ratio [26]. In addition, compression of the umbilical cord shifts down blood flow velocity profiles in the DV, increasing dramatically the pulsatility index of this vessel [26].

To study the regulation of the DV inlet in vivo, Kiresud and colleagues measured the effects of vasoactive substances and hypoxemia on its diameter in nine fetal sheep in utero at 0.9 gestation under ketamine-diazepam anesthesia [25]. Hypoxemia caused a 61% increase of the inlet diameter and a distension of the entire DV, suggesting that the DV inlet is under active regulation, demonstrated by its distension during infusion of an NO donor or hypoxemia [25]. This observation has never been demonstrated in humans, and therefore, the presence of a sphincter in the trajectory of the DV remains controversial.

### **Fetal ductus venosus flow assessment in daily clinical practice**

Doppler ultrasound is the technology of current use in daily clinical practice for the evaluation of the fetal DV waveform. In the recent years, as a result of the

technological evolution in this area, especially in the quality and resolution of the ultrasound systems, Doppler ultrasound has proven to be an excellent technology for non-invasive evaluation of the fetal circulation. In particular, DV evaluation is a technique that requires training and should be used for clinical decisions when it is performed by trained and properly certified operators. In fact, competence in Doppler assessment of the DV is achieved only after extensive supervised training [34].

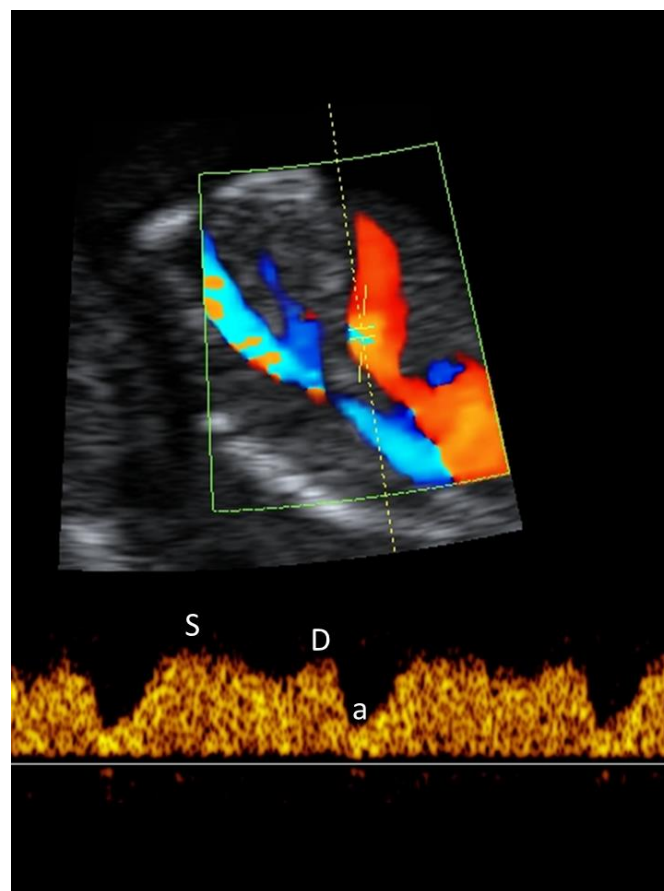


Figure 2. Color Doppler imaging of the ductus venosus (DV) and a normal first-trimester DV waveform.

The evaluation of the DV flow can be made in the first [35-40] or second and third trimesters of pregnancy [41-49] (Figures 2 and 3). The DV can be visualized in a mid-sagittal longitudinal plane of the fetal trunk or in an oblique transverse plane through

the upper abdomen [50]. According to the Fetal Medicine Foundation protocol [51], DV examination should be undertaken during fetal quiescence, in the absence of fetal movements. For an adequate observation of the DV, the magnification of the image should be such that the fetal thorax and abdomen occupy the whole image, and a right ventral mid-sagittal view of the fetal trunk should be obtained [51]. Color flow mapping should be undertaken to demonstrate the umbilical vein, DV and fetal heart [51]. This protocol suggests that the pulsed Doppler sample volume should be small (0.5-1.0 mm in the first trimester and 1.0-2.0 mm in the second and third trimesters) to avoid contamination from the adjacent veins, and it should be placed in the yellowish aliasing area. The insonation angle should be less than 30 degrees and the filter should be set at a low frequency (50-70 Hz) so that the a-wave is not obscured. The sweep speed should be high (2-3 cm/s) so that the waveforms are spread, allowing better assessment of the a-wave [51]. When these criteria are satisfied, it is possible to assess the a-wave and determine qualitatively whether the flow is positive, absent or reversed. The DV pulsatility index (DV-PIV), which is the Doppler ratio most utilized in daily clinical practice for impedance assessment of the DV, is measured by the machine after manual tracing of the outline of the waveform [51].

It is important to remember that the peak systolic velocity increases from 48 cm/s at 14 weeks to 71 cm/s at 41 weeks; therefore, the spectrum obtained by Doppler ultrasound should be in agreement with previously published reference curves [50,52-55]. This is particularly relevant because of the similarity between DV waveforms and suprahepatic veins, which are in a satellite location to the DV and can be easily confused with the DV spectra. The DV exhibits a normal flow-velocity profile that is

typically antegrade throughout the entire cardiac cycle [56]. This feature is permissive to the semi-quantitative evaluation of its complex waveform.

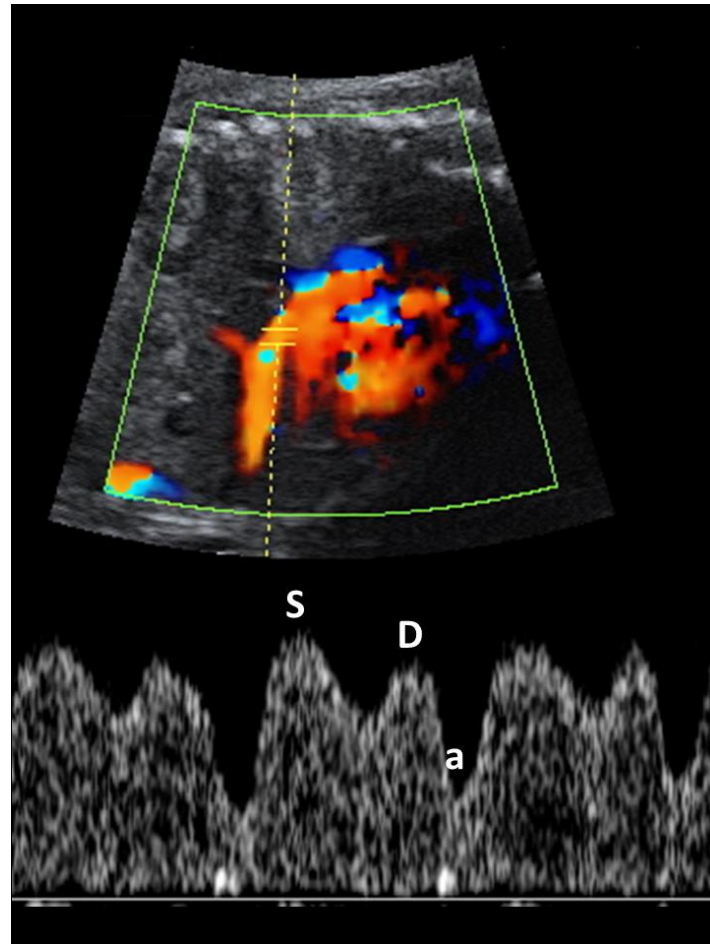


Figure 3. Color Doppler imaging of the ductus venosus (DV) and a normal second-trimester DV waveform.

The denomination of the phases that make up the DV venous flow-velocity waveform is closely related to the respective period of the cardiac cycle. In normal conditions, the cardiac cycle involves five distinct phases: early diastole, atrial contraction, isovolumetric contraction, ejection phase, and isovolumetric relaxation. During the isovolumetric contraction phase of the cardiac cycle, the ventricular pressure rises steeply with no change in ventricular volume as both the



atrioventricular and semilunar valves are closed [57]. As the ventricular pressure continues to rise, it exceeds the pressure within the great arteries, and the semilunar valves open, resulting in rapid ejection of blood [57]. With ventricular ejection, myocardial deformation ensues, and this phase is associated with a drop in ventricular volume and pressure [57]. With the initiation of ventricular systole, the descent of the atrioventricular valve ring decreases atrial pressure and increases the amount of venous return that can be accommodated by the atria [56]. This produces the first increase in venous forward velocities, which peak at the S-wave [56] (Figure 2/3). As the ventricular pressure drops below the pressure within the great arteries, the semilunar valves close [57]. A period of isovolumetric relaxation ensues, which is associated with decreased ventricular pressure with no change in ventricular volume as the atrioventricular valves are closed [57]. At this time, the AV valve ring ascends towards its resting position, atrial pressures rise, and venous forward velocities fall to the first trough, designated the v-descent. As the ventricular pressure decreases below that of the atria, the atrioventricular valves open [57], and the higher pressures in the atria lead to an opening of the AV valves, allowing for an increase in venous forward velocities towards the second peak during passive diastolic ventricular filling (D-wave) [56] (Figure 2/3). The atrial contraction occurs in late diastole and results in complete filling of the ventricles, promoting a slight increase in ventricular pressure [57]. During the isovolumetric contraction phase of the cardiac cycle, ventricular pressure rises steeply with no change in ventricular volume as both the atrioventricular and semilunar valves are closed [57]. The fall in venous forward velocities produces the second trough, designated the a-wave [56] (Figure 1,2). Although the correlation between the DV waveform and the phases of the cardiac cycle can be established temporally, there is no experimental evidence for a direct

correlation between DV waveform and fetal heart function. Nevertheless, the continuity of venous forward flow fluctuates with the capacity of the heart to accommodate venous return, which depends on venous volume (preload), cardiac function (relaxation, compliance and contractility) and downstream arterial blood-flow resistance (afterload) [58]. In other words, DV blood velocity reflects the portocaval pressure gradient that drives this flow in addition to the portal liver perfusion, as assumed previously [53,59]. However, this gradient must be modulated by adequate cardiac compliance, which varies according to the gestational age and in some fetal pathological conditions. Given that an umbilicocaval (portocaval) pressure gradient is the driving pressure for perfusing the liver and for causing the umbilical blood to reach the foramen ovale, it was assumed, in the construction of recent longitudinal reference ranges [53], that the peak systolic velocity or velocities close to this reflected the optimal perfusion pressure in the individual fetus [53].

In daily clinical practice, an abnormal flow in DV is easily identified, qualitatively, by observing the absence or inversion of the a-wave. In these cases, the pulsatility index increases significantly, translating a significant increase in the pressure gradient towards the right atrium. Nevertheless, it is important to keep in mind that, during atrial systole, the venous blood column is in continuity with the right atrium, but this atrium is in continuity with the left atrium and right ventricle. For this reason, the identification of an abnormal DV waveform requires a careful examination of the fetal cardiovascular system, including the placental circulation, because multiple mechanisms of disease can coexist. The evaluation should be done in a systematic way and should be morphological and functional in order to rule out pathological

conditions such as increased cardiac preload, abnormal cardiac structure and function, and increased cardiac afterload.

### **Ductus venosus Doppler to screening of cardiac defects**

Congenital heart defects are the most commonly occurring congenital malformations that cause significant mortality and morbidity. For this reason, the interest in the early detection of this set of pathologies is a cause of concern for all those dedicated to prenatal diagnosis. In particular, visualization of the fetal heart with adequate echographic resolution is only possible from the end of the first trimester, and therefore, the identification of risk markers for the occurrence of congenital heart defects deserves the full commitment of the sonographers. Growing evidence suggests that assessment of DV flow improves the performance of nuchal translucency (NT) screening for cardiac defects.

With the objective to evaluate in a meta-analysis of the screening performance of abnormal DV Doppler waveforms for detection of congenital heart disease (CHD) in chromosomally normal fetuses, a group of authors analyzed seven studies regardless of the NT status, nine studies with increased NT and seven studies with normal NT [60]. In populations including participants regardless of NT status, the summary sensitivity and specificity of DV for detecting CHD were 50 and 93%, respectively [60]. In participants with increased NT, the summary sensitivity and specificity were 83 and 80%, and in those with normal NT, the summary sensitivity and specificity were 19 and 96%, respectively [60]. The findings of this meta-analysis on chromosomally normal fetuses demonstrate that the DV waveform examination has moderate sensitivity for detecting CHD [60]. However, the authors concluded that DV

assessment for the detection of CHD in chromosomally normal fetuses can be considered in evaluating the potential use and limitations of this screening test (Papatheodorou et al., 2011). These results are consistent with more recent evidence suggesting that in chromosomally normal fetuses, the addition of an abnormal DV a-wave to increased NT does not improve the screening performance of NT in the detection of major hearts defects in the first trimester [61].

In conclusion, in fetuses with normal NT, the sensitivity of this marker is not strong enough to be used as a screening test for CHD [62]. Additionally, because there are some small differences in the DV flow of T21 fetuses with and without CHD, DV flow is not clinically useful in this group of patients [63]. Further investigations are needed to enhance the clinical utility of the DV in association with other markers of CHD in high-risk pregnancies [64,65].

### **Ductus venosus Doppler contribution to screen for chromosomal defects**

NT screening combined with maternal age at early mid-trimester can identify approximately 75% of chromosomal abnormalities, with a false-positive rate of 5% [67]. To improve the test performance, Doppler parameters have been included in the screening of fetal chromosomal abnormalities. In the first trimester, a reversed a-wave is associated with an increased risk for chromosomal abnormalities [68] and fetal death [69] in singleton and twin pregnancies [70]. However, in approximately 80% of cases with a reversed a-wave, the pregnancy outcome is normal [69]. Combining the DV-PIV and NT, overall sensitivity decreased to 55%, but specificity reached 99.3%, with a negative predictive value of 99.3% [71]. Because changes in the DV-PIV can be found in fetuses with chromosomal abnormalities, with or without cardiac defects, and in those with certain

cardiac abnormalities with normal karyotypes, the DV-PIV should not be used as a first-line screening test at 10–16 weeks of gestation [71]. Although the DV-PIV does not increase the number of cases detected by NT, it can be useful as a second-line test in screen-positive cases with NT in order to increase the specificity, reducing the need for invasive testing [8,71]. Additionally, because DV blood flow pattern is correlated with the nuchal translucency measurement, it cannot be used as an independent variable to reduce the indication for fetal karyotyping [72].

### **Ductus venosus Doppler in the management of intrauterine growth restriction**

Decreased, absent, or reversed flow in the a-wave of the DV may represent myocardial impairment and increased ventricular end-diastolic pressure resulting from an increase in right ventricular afterload. This abnormal DV waveform has been documented in fetuses with intrauterine growth restriction (IUGR) and linked to an increased neonatal acidemia and perinatal mortality [66].

Recently, in a sheep model of increased placental vascular resistance, a group of authors investigated whether hypoxemia without acidemia affects the DV blood velocity waveform pattern in sheep fetuses with an intact placenta and whether worsening acidemia and impending fetal death are related to changes in DV velocimetry in fetuses with increased placental vascular resistance [73]. The principal conclusion of this important experimental study was that fetal hypoxemia increases the pulsatility of the DV blood velocity waveform pattern [73]. However, in fetuses with elevated placental vascular resistance, DV pulsatility does not increase further in the presence of severe and worsening fetal acidemia and impending fetal death [73]. The authors state that fetal hypoxemia can increase

pulsatility in the DV blood velocity waveform pattern [73]. However, it appears that it cannot recognize those ovine fetuses that will become acidemic and even die within a short time period [73], suggesting that the development of an abnormal DV blood flow pattern requires additional pathophysiological events that lead to increased ventricular end-diastolic and systemic venous pressures [73]. In human fetuses, the duration of absent or reversed flow during atrial systole in the DV is a strong predictor of stillbirth that is independent of gestational age [74].

Although a progressive predictable sequence of placental and fetal Doppler changes has been described as an adaptive mechanism to a suboptimal intrauterine environment in pregnancies affected by IUGR, the optimal surveillance pattern and timing of delivery remain the focus of much debate and research, with no internationally accepted approach to management [75]. With the objective to assess whether changes in the fetal DV Doppler waveform could be used as indications for delivery instead of cardiotocography (CTG), an extensive randomized study (including women with singleton fetuses at 26-32 weeks of gestation who had very preterm fetal growth restriction) found that when the timing of delivery was based on the study protocol using late changes in the DV waveform, the results exhibited an improvement in the developmental outcomes at 2 years of age [76,77]. Although assuming that the optimal management of early IUGR fetuses should integrate clinical, Doppler, and CTG parameters, the authors caution that severe anomalies in the DV, when they precede CTG abnormalities, are an indication for undertaking delivery [77].

## **Ductus venosus Doppler contribution to screening of monochorionic twin complications**

Ultrasonography is central to the proper diagnosis of the type of twinning (Smith et al., 2018). Monochorionic twin pregnancies are at increased risk for adverse outcomes compared to dichorionic twin pregnancies and singletons, including twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence, single intrauterine fetal demise and its consequences on the co-twin, and selective intrauterine growth restriction [78]. In particular, TTTS is associated with significant mortality and morbidity [79].

Several studies have assessed the role of first- and early second-trimester markers in the prediction of TTTS in monochorionic twin pregnancies [80] because DV flow profiles and the timing of waveform events are already altered in preTTTS and in the early-stage disease [81]. As a corollary of an extensive meta-analysis that included approximately 2000 pregnancies, of which 323 developed TTTS, an increased risk of TTTS was associated with intertwin NT discrepancy (positive likelihood ratio (LR+), 1.92 (95% CI, 1.25-2.96); a negative likelihood ratio (LR-), 0.65 (95% CI, 0.50-0.84)); NT > 95<sup>th</sup> percentile (LR+, 2.63 (95% CI, 1.51-4.58); LR-, 0.85 (95% CI, 0.75-0.96)); CRL discrepancy > 10% (LR+, 1.80 (95% CI, 1.05-3.07); LR-, 0.92 (95% CI, 0.81-1.05)); and abnormal DV flow (LR+, 4.77 (95% CI, 1.33-17.04; LR-, 0.49 (95% CI, 0.17-1.41)) [80]. The highest sensitivities were observed for intertwin NT discrepancy >10% (52.8% (95% CI, 43.8-61.7%)) and abnormal DV flow (50.0% (95% CI, 33.4-66.6%)) [80]. Additionally, unbalanced blood volume in TTTS led to alterations in the time intervals of DV, suggesting that the assessment of DV Doppler

velocimetry will provide detailed information on fetal cardiac function before and after laser therapy [82].

### **Agenesis of the ductus venosus**

Congenital absence of the DV (ADV) is a rare vascular anomaly with a controversial prevalence. Prognosis largely depends on other fetal cardiac and extra-cardiac anomalies, chromosomopathies, the presence of effusions/hydrops fetalis and the pattern of umbilical venous drainage associated.

There are three main patterns of drainage. If the umbilical vein bypasses the liver, it leads to an increased and unregulated flow into the right atrium (46%), putting this fetus at risk of developing cardiomegaly; this can result in high-output cardiac failure and hydrops. The umbilical vein can also bypass the liver and connect to the inferior vena cava by one iliac or renal vein (26%), causing hyperperfusion of the liver sinusoids and portal hypertension and hydrops. Lastly, the umbilical vein may connect to the portal circulation without giving rise to the DV (21%) [83,84].

Therefore, when ADV is detected, a more detailed fetal examination and the detection of other anomalies is often necessary.

The exact etiology of ADV is unclear, and it may result from primary agenesis and/or functional or structural closure. Usually, ADV can be detected during the early scan of the first trimester evaluation [85], but in some cases, the ultrasound scan is reported as normal in early pregnancy; there can be a missed diagnosis, but another explanation is the formation of a secondary closure due to an unknown gradual condition [86]. ADV can appear associated with varying comorbidities, some of



which are incompatible with life: cardiomegaly, chromosomopathies, altered fetal growth and hepatic calcifications [87]. It was reported [84] that the overall survival rate was 60% and only 50% when the ADV was associated with effusions/hydrops. However, if there was no evidence of hydrops and cardiac overload associated with the ADV, the survival rate was 100%, regardless of the type of ADV [84]. In fact, many studies report a good outcome when there is no further pathological finding, as chromosomopathy or hydrops [84,85,88]. Fetuses with ADV and restrictive alternative umbilical venous pathways may have a more benign clinical course because the “small shunt” is unlikely to induce cardiac failure [88]. Not only the caliber of the shunt but also the NT thickness seems to be important in the evaluation of the prognosis, unless ADV appears isolated [85,88].

Postnatally, cessation of umbilical venous flow occurs, and the short-term impact does not appear to be significant [84], with a regression of the anomaly [88].

However, ADV may lead to significant long-term complications if associated with particular fetal anomalies, such as portal vein agenesis with extrahepatic umbilical vein drainage or congenital absence of the portal venous system. Although ADV with intrahepatic drainage is associated with better chances of survival, infants with congenital absence of the portal venous system, complicated with intrahepatic drainage, have a potentially serious condition [86].

Fetal echocardiography, with access to detailed anatomy, and fetal karyotyping are recommended actions when ADV is noticed (Thomas et al., 2012). The ultrasound plays an important role not only in detecting abnormalities that can help dictate the prognosis but also allowing parental counseling.

## **Patent ductus venosus**

Patent DV (PDV) is a rare congenital condition where the DV persists as a portosystemic shunt connecting the portal system and inferior vena cava [89-91].

A DV flow effect in neonatal liver and its persistence after birth remain an unclear subject [90-92]. Few cases have been described so far, and diagnoses occurred not only in early childhood but also in adulthood or even on autopsy studies [93-96]. The majority appear sporadic, but a recessive genetic heritage has been hypothesized since the description of PDV in three brothers [89].

DV blood flow influences important liver functions in early neonates, such as ammonia detoxification, coagulation and serum bile acid concentration [97]. When this portosystemic communication persists, hepatic atrophy and hepatic failure will develop, and biochemical markers include hypergalactosemia, hyperbilirubinemia, hyperammonemia, an increased coagulation time and an augmented serum bile acid concentration. Thereafter, presentation of PDV includes systemic manifestations, representing hepatic, pulmonary and cardiac dysfunction [97-99]. Manifestations reported include cholestatic jaundice [93-100], hepatic encephalopathy [91,94,95,99], massive gastrointestinal bleeding [98]; acute liver failure [99,101]; respiratory distress [102] and pulmonary arteriovenous fistulae [103,104], and tumor-like hepatic lesions [92,105]. A child with a single ventricle, who presented with spontaneous microbubbles on echocardiography, was found to have a PDV [106]. Other peculiar associations have been reported. Yamaguchi et al. presented a girl with Down syndrome who was diagnosed with PDV after neonatal cholestasis and a transient abnormal myeloproliferative disorder [100]. Sagiv-Friedgut et al. questioned a

genetically linked association of PDV and immunoglobulin E syndrome after their description of these conditions in a pair of siblings [107]. An association between PDV and autoimmune disorders was noted by Yashimoto et al. [102]. Acute liver failure has been associated not only with PDV but also with Enterovirus infection and neonatal hemochromatosis [99,101]. One case of Budd-Chiari syndrome has been associated with PDV and confirmed only in autopsy [96].

Given these pleiotropic presentations, diagnosis may be challenging. Usually, biochemical alterations suggest a hepatic disorder, and a liver ultrasound or abdominal computed tomography (with or without angiographic study) is performed. This may reveal or at least raise the suspicion of a portosystemic shunt [91,94,95,97,99,102,103,105,106]. Magnetic resonance angiography has also been suggested as an important diagnostic tool, specifically for infants [108].

Most cases improve substantially with anomalous shunt closure by surgical ligation (via laparotomy or laparoscopy) or embolization using a vascular plug through interventional radiology [90,91,93-95,98,99,101-104].

## **Conclusion**

In conclusion, the DV acts as a bypass of the liver microcirculation and plays a critical role in the fetal circulation. The DV allows oxygenated and nutrient-rich venous blood to flow from the placenta to the myocardium and brain. Increased impedance to flow in the fetal DV is associated with fetal aneuploidies, cardiac defects and other adverse pregnancy outcomes. Further research is necessary to

determine the importance of the DV Doppler assessment in improving perinatal outcomes.

### **List of Abbreviations**

ADV, congenital absence of the ductus venosus

CHD, congenital heart disease

CTG, cardiotocography

DV, ductus venosus

DV-PIV, ductus venosus pulsatility index

IUGR, intrauterine growth restriction

NT, nuchal translucency

PDV, patent ductus venosus

T21, Trisomy 21

TGF- $\beta$ , transforming growth factor  $\beta$

TTTS, twin-twin transfusion syndrome

UV, umbilical vein

VEGF, of vascular endothelial growth factor

VS, vasculogenesis

### **Ethics Committee Approval**

N/A

### **Peer-review**

Externally peer-reviewed.

### **Author Contributions**

Concept – M.B., L.G.-M.; Design – M.B., L.G.-M.; L.M.; Supervision – L.G.-M.; Literature Review – M.B., L.G.-M.; Writer – M.B., L.G.-M.; L.M.; Critical Review – L.G.-M., M.B.

### **Conflicts of Interest**

We have no conflicts of interest in this review.

### **Acknowledgements**

The staff of the Department of Obstetrics of Centro Hospitalar do Porto is acknowledged.

### **Financial Disclosure**

The authors declared that this study received no financial support.

### **References**

1. Kiserud T, Eik-Nes SH, Blaas HG, Hellevik LR. Ultrasonographic velocimetry of the fetal ductus venosus. *Lancet*. 1991 Dec 7;338(8780):1412-4.
2. Kiserud T. The ductus venosus. *Semin Perinatol*. 2001 Feb;25(1):11-20.
3. Tchirikov M, Schröder HJ, Hecher K. Ductus venosus shunting in the fetal venous circulation: regulatory mechanisms, diagnostic methods and medical importance. *Ultrasound Obstet Gynecol*. 2006 Apr;27(4):452-61.

4. Kiserud T, Acharya G. The fetal circulation. *Prenat Diagn.* 2004 Dec 30;24(13):1049-59.
5. Tchirikov M, Schlabritz-Loutsevitch NE, Hubbard GB, Nathanielsz PW, Beindorff N, Schroder HJ. Ductus venosus shunting in marmoset and baboon fetuses. *Ultrasound Obstet Gynecol* 2005; 26: 252 – 257
6. Matias A, Hugon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10-14 weeks. *Ultrasound Obstet Gynecol.* 1999 Nov;14(5):307-10.
7. Matias A, Montenegro N, Areias JC, Leite LP. Haemodynamic evaluation of the first trimester fetus with special emphasis on venous return. *Hum Reprod Update.* 2000 Mar-Apr;6(2):177-89.
8. Matias A, Montenegro N. Ductus venosus blood flow in chromosomally abnormal fetuses at 11 to 14 weeks of gestation. *Semin Perinatol.* 2001 Feb;25(1):32-7.
9. Matias A, Montenegro N, Loureiro T, et al. Screening for twin-twin transfusion syndrome at 11-14 weeks of pregnancy: the key role of ductus venosus blood flow assessment. *Ultrasound Obstet Gynecol.* 2010 Feb;35(2):142-8.
10. Byrd N, and Grabel L: Hedgehog signaling in murine vasculogenesis and angiogenesis. *Trends Cardiovasc Med* 2004; 14: pp. 308-313
11. Eric D. Endean, Bruce E. Maley. *Rutherford's Vascular Surgery* / [edited by] Jack L. Cronenwett, K. Wayne Johnston, by Saunders, an imprint of Elsevier Inc., Eighth Edition, 2014, Chapter 2, 15-33.
12. Zhan W, et al: Regulation of Hex gene expression and initial stages of avian hepatogenesis by Bmp and Fgf signaling. *Dev Biol* 2004; 268: pp. 312-326

13. Red-Horse K, Crawford Y, Shojaei F, Ferrara N. Endothelium microenvironment interactions in the developing embryo and in the adult. *Dev Cell*. 2007 Feb;12(2):181-94.
14. Adams RH, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. *Nat Rev Mol Cell Biol*. 2007 Jun;8(6):464-78.
15. Tchirikov M, Rybakowski C, Huneke B, Schröder HJ. Blood flow through the ductus venosus in singleton and multifetal pregnancies and in fetuses with intrauterine growth retardation. *Am J Obstet Gynecol* 1998; 178: 943 – 949
16. Bellotti M, Pennati G, De Gasperi C, Bozzo M, Battaglia FC, Ferrazzi E. Simultaneous measurements of umbilical venous, fetal hepatic, and ductus venosus blood flow in growth-restricted human fetuses. *Am J Obstet Gynecol* 2004; 190: 1347 – 1358
17. Power GG, Longo LD. Fetal circulation times and their implications for tissue oxygenation. *Gynecol Invest* 1975; 6: 342 – 355.
18. Edelstone DI, Rudolph AM, Heymann MA. Effects of hypoxemia and decreasing umbilical flow liver and ductus venosus blood flows in fetal lambs. *Am J Physiol* 1980; 238: H656 – 663.
19. Reuss ML, Rudolph AM. Distribution and recirculation of umbilical and systemic venous blood flow in fetal lambs during hypoxia. *J Dev Physiol* 1980; 2: 71 – 84.
20. Itskovitz J, Goetzman BW, Rudolph AM. Effects of hemorrhage on umbilical venous return and oxygen delivery in fetal lambs. *Am J Physiol* 1982; 242: H543 – 548.
21. Itskovitz J, LaGamma EF, Rudolph AM. Effects of cord compression on fetal blood flow distribution and O<sub>2</sub> delivery. *Am J Physiol* 1987; 252: H100 – 109.

22. Paulick RP, Meyers RL, Rudolph CD, Rudolph AM. Venous responses to hypoxemia in the fetal lamb. *JDevPhysiol* 1990; 14: 81 – 88.
23. Paulick RP, Meyers RL, Rudolph CD, Rudolph AM. Umbilical and hepatic venous responses to circulating vasoconstrictive hormones in fetal lamb. *Am J Physiol* 1991; 260: H1205 – 1213.
24. Jensen A, Roman C, Rudolph AM. Effects of reducing uterine blood flow on fetal blood flow distribution and oxygen delivery. *JDevPhysiol* 1991; 15: 309 – 323.
25. Kiserud T, Ozaki T, Nishina H, Rodeck C, Hanson MA. Effect of NO, phenylephrine, and hypoxemia on ductus venosus diameter in fetal sheep. *Am J Physiol* 2000a; 279: H1166 – 1171.
26. Tchirikov M, Hecher K, Deprest J, Zikulnig L, Devlieger R, Schröder HJ. Doppler ultrasound measurements in the central circulation of anesthetized fetal sheep during obstruction of umbilical – placental blood flow. *Ultrasound Obstet Gynecol* 2001; 18: 656 – 661.
27. Behrman RE, Lees MH, Peterson EN, De Lannoy CW, Seeds AE. Distribution of the circulation in the normal and asphyxiated fetal primate. *Am J Obstet Gynecol* 1970; 108: 956 – 969
28. Paton JB, Fisher DE, DeLannoy CW, Behrman RE. Umbilical blood flow, cardiac output, and organ blood flow in the immature baboon fetus. *Am J Obstet Gynecol* 1973; 117: 560 – 566.
29. Rudolph AM, Heymann MA, Teramo KAW, Barrett CT, Raiha NCR. Studies on the circulations of the previable human fetus. *Pediatr Res* 1971; 5: 452 – 465
30. Kiserud T, Rasmussen S, Skulstad S. Blood flow and the degree of shunting through the ductus venosus in the human fetus. *Am J Obstet Gynecol* 2000a; 182: 147 – 153.



31. Bellotti M, Pennati G, De Gasper iC, Battaglia FC, Ferrazzi E. Role of ductus venosus in distribution of umbilical blood flow in human fetuses during second half of pregnancy. *Am J Physiol Heart Circ Physiol* 2000; 279: H1256 – 1263.
32. Haugen G, Kiserud T, Godfrey K, Crozier S, Hanson M. Portal and umbilical venous blood supply to the liver in the human fetus near term. *Ultrasound Obstet Gynecol* 2004; 24: 599 – 605
33. Tchirikov M, Eisermann K, Rybakowski C, Schröder HJ. Doppler ultrasound evaluation of ductus venosus blood flow during acute hypoxemia in fetal lambs. *Ultrasound Obstet Gynecol* 1998; 11: 426 – 431.
34. Maiz N, Kagan KO, Milovanovic Z, Celik E, Nicolaides KH. Learning curve for Doppler assessment of ductus venosus flow at 11 + 0 to 13 + 6 weeks' gestation. *Ultrasound Obstet Gynecol*. 2008 May;31(5):503-6.
35. Gürses C. How to get ductus venosus flow velocity waveforms between 11 and 14 weeks: Candle Flame and Falling Drop Signs. *Med Ultrason*. 2016 Dec 5;18(4):528-529.
36. Wiechec M, Nocun A, Matyszkiewicz A, Wiercinska E, Latała E. First trimester severe ductus venosus flow abnormalities in isolation or combination with other markers of aneuploidy and fetal anomalies. *J Perinat Med*. 2016 Mar;44(2):201-9.
37. Kagan KO, Wright D, Nicolaides KH. First-trimester contingent screening for trisomies 21, 18 and 13 by fetal nuchal translucency and ductus venosus flow and maternal blood cell-free DNA testing. *Ultrasound Obstet Gynecol*. 2015 Jan;45(1):42-7.
38. Togrul C, Ozaksit GM, Seckin KD, Baser E, Karsli MF, Gungor T. Is there a role for fetal ductus venosus and hepatic artery Doppler in screening for fetal aneuploidy in the first trimester? *J Matern Fetal Neonatal Med*. 2015;28(14):1716-9.

39. Florjański J, Fuchs T, Zimmer M, Homola W, Pomorski M, Blok D. The role of ductus venosus Doppler flow in the diagnosis of chromosomal abnormalities during the first trimester of pregnancy. *Adv Clin Exp Med*. 2013 May-Jun;22(3):395-401.
40. Sabria J, Comas C, Barceló-Vidal C, et al. Cumulative sum plots and retrospective parameters in first-trimester ductus venosus quality assurance. *Prenat Diagn*. 2013 Apr;33(4):384-90.
41. Karakoç G, Yavuz A, Eriş Yalçın S, Akkurt MÖ, Danişman N. The significance of reverse flow in ductus venosus between sixteen and twenty weeks' gestation. *Turk J Obstet Gynecol*. 2017 Mar;14(1):23-27.
42. Suksai M, Suwanrath C, Kor-Anantakul O, Geater A. Time Interval Measurements of the Ductus Venosus During the Early Second Trimester of Pregnancy: Reference Ranges and Clinical Application. *J Ultrasound Med*. 2018 Mar;37(3):745-753.
43. Pokharel P, Ansari MA. Fetal Ductus Venosus Pulsatility Index and Diameter during Second and Third Trimester of Gestation. *JNMA J Nepal Med Assoc*. 2017 Jan-Mar;56(205):124-131.
44. İlhan G, İyibozkurt AC, Kalelioğlu Hİ, et al. Effects of fetal cardiac anomalies on ductus venosus and aortic isthmus doppler profiles. *Arch Gynecol Obstet*. 2016 Feb;293(2):345-50.
45. Martins WP, Kiserud T. How to record ductus venosus blood velocity in the second half of pregnancy. *Ultrasound Obstet Gynecol*. 2013 Aug;42(2):245-6.
46. Demirturk F, Caliskan AC, Aytan H, Sahin S. A preliminary retrospective study about the relationship between ductus venosus Doppler indices, nuchal translucency (NT) and biochemical markers in the first and second trimester screening tests. *Gynecol Endocrinol*. 2012 May;28(5):378-81.

47. Tongprasert F, Srisupundit K, Luewan S, Wanapirak C, Tongsong T. Normal reference ranges of ductus venosus Doppler indices in the period from 14 to 40 weeks' gestation. *Gynecol Obstet Invest.* 2012;73(1):32-7.
48. Stressig R, Kozlowski P, Froehlich S, et al. Assessment of the ductus venosus, tricuspid blood flow and the nasal bone in second-trimester screening for trisomy 21. *Ultrasound Obstet Gynecol.* 2011 Apr;37(4):444-9.
49. Hung JH, Fu CY, Lu JH, Hung CY. Ductus venosus blood flow resistance and congenital heart defects in the second trimester. *J Clin Ultrasound.* 2008 Feb;36(2):72-8.
50. Hecher K, Campbell S, Snijders R, Nicolaides K. Reference ranges for fetal venous and atrioventricular blood flow parameters. *Ultrasound Obstet Gynecol.* 1994 Sep 1;4(5):381-390.
51. Fetal Medicine Foundation. Available at <https://fetalmedicine.org/fmf-certification/certificates-of-competence/ductus-venosus-flow>. Accessed October 30, 2017.
52. Teixeira LS, Leite J, Viegas MJ, et al. Ductus venosus Doppler velocimetry in the first trimester: a new finding. *Ultrasound Obstet Gynecol.* 2008 Mar;31(3):261-5.
53. Kessler J, Rasmussen S, Hanson M, Kiserud T. Longitudinal reference ranges for ductus venosus flow velocities and waveform indices. *Ultrasound Obstet Gynecol.* 2006 Dec;28(7):890-8.
54. Prefumo F, Risso D, Venturini PL, De Biasio P. Reference values for ductos venosus Doppler flow measurements at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol.* 2002 Jul;20(1):42-6.

55. Bahlmann F, Wellek S, Reinhardt I, Merz E, Steiner E, Welter C. Reference values of ductus venosus flow velocities and calculated waveform indices. *Prenat Diagn.* 2000 Aug;20(8):623-34.
56. Baschat AA, Turan OM, Turan S. Ductus venosus blood-flow patterns: more than meets the eye? *Ultrasound Obstet Gynecol.* 2012 May;39(5):598-9.
57. Abuhamad A, Chaoui R. Foetal cardiac function. In: Abuhamad A, Chaoui R. A practical guide to foetal echocardiography. 3<sup>rd</sup> ed. Wolters Kluwer 2016; pp.178-186.
58. Sanapo L, Turan OM, Turan S, Ton J, Atlas M, Baschat AA. Correlation analysis of ductus venosus velocity indices and fetal cardiac function. *Ultrasound Obstet Gynecol.* 2014 May;43(5):515-9.
59. Kiserud T, Hellevik LR, Eik-Nes SH, Angelsen BA, Blaas HG. Estimation of the pressure gradient across the fetal ductus venosus based on Doppler velocimetry. *Ultrasound Med Biol* 1994; 20: 225 – 232.
60. Papatheodorou SI, Evangelou E, Makrydimas G, Ioannidis JP. First-trimester ductus venosus screening for cardiac defects: a meta-analysis. *BJOG.* 2011 Nov;118(12):1438-45.
61. Karadzov-Orlic N, Egic A, Filimonovic D, Damnjanovic-Pazin B, Milovanovic Z, Lukic R, Mandic V, Joksic I, Vukomanovic V, Kosutic J, Djuricic S, Mikovic Z. Screening performances of abnormal first-trimester ductus venosus blood flow and increased nuchal translucency thickness in detection of major heart defects. *Prenat Diagn.* 2015 Dec;35(13):1308-15.
62. Prats P, Ferrer Q, Comas C, Rodríguez I. Is the addition of the ductus venosus useful when screening for aneuploidy and congenital heart disease in fetuses with normal nuchal translucency? *Fetal Diagn Ther.* 2012;32(1 2):138-43

63. Wagner P, Sonek J, Eberle K, et al. First trimester screening for major cardiac defects based on the ductus venosus flow in fetuses with trisomy 21. *Prenat Diagn*. 2018 Apr 16.
64. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev*. 2017 Jun 13;6:CD007529.
65. Cheema R, Bayoumi MZ, Gudmundsson S. Multivascular Doppler surveillance in high risk pregnancies. *J Matern Fetal Neonatal Med*. 2012 Jul;25(7):970-4.
66. Baschat AA. Ductus venosus Doppler for fetal surveillance in high risk pregnancies. *Clin Obstet Gynecol*. 2010 Dec;53(4):858-68.
67. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. *Am J Obstet Gynecol*. 2004 Jul;191(1):45-67.
68. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: the role of ductus venosus blood flow. *Ultrasound Obstet Gynecol*. 1998 Dec;12(6):380-4.
69. Maiz N, Valencia C, Emmanuel EE, Staboulidou I, Nicolaides KH. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11-13+6 weeks of gestation. *Obstet Gynecol*. 2008 Sep;112(3):598-605.
70. Maiz N, Nicolaides KH. Ductus venosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. *Fetal Diagn Ther*. 2010;28(2):65-71.
71. Antolín E, Comas C, Torrents M, et al. The role of ductus venosus blood flow assessment in screening for chromosomal abnormalities at 10-16 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001 Apr;17(4):295-300.
72. Bilardo CM, Müller MA, Ziklunig L, Schipper M, Hecher K. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship

- with nuchal translucency measurement and fetal outcome. *Ultrasound Obstet Gynecol.* 2001 Apr;17(4):288-94.
73. Mäkikallio K, Acharya G, Erkinaro T, et al. Ductus venosus velocimetry in acute fetal acidemia and impending fetal death in a sheep model of increased placental vascular resistance. *Am J Physiol Heart Circ Physiol.* 2010 Apr;298(4):H1229-34.
74. Turan OM, Turan S, Berg C, Gembruch U, Nicolaides KH, Harman CR, Baschat AA. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. *Ultrasound Obstet Gynecol.* 2011 Sep;38(3):295-302.
75. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Predictable progressive Doppler deterioration in IUGR: does it really exist? *Am J Obstet Gynecol.* 2013 Dec;209(6):539.e1-7.
76. Lees CC, Marlow N, van Wassenae-Leemhuis A, et al; TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet.* 2015 May 30;385(9983):2162-72.
77. Frusca T, Todros T, Lees C, Bilardo CM; TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized foetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. *Am J Obstet Gynecol.* 2018 Feb;218(2S):S783-S789.
78. Djaafri F, Stirnemann J, Mediouni I, Colmant C, Ville Y. Twin-twin transfusion syndrome - What we have learned from clinical trials. *Semin Fetal Neonatal Med.* 2017 Dec;22(6):367-375.

79. Perry H, Duffy JMN, Umadia O, Khalil A; International Collaboration to Harmonise Outcomes for Twin-Twin Transfusion Syndrome (CHOOSE). Outcome reporting across randomised trials and observational studies evaluating treatments for Twin-Twin Transfusion Syndrome: a systematic review. *Ultrasound Obstet Gynecol.* 2018 Apr 1.
80. Stagnati V, Zanardini C, Fichera A, Pagani G, Quintero RA, Bellocco R, Prefumo F. Early prediction of twin-to-twin transfusion syndrome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2017 May;49(5):573-582.
81. Wohlmuth C, Boudreaux D, Moise KJ Jr, Johnson A, Papanna R, Bebbington M, Gardiner HM. Cardiac pathophysiology in twin-twin transfusion syndrome: new insights into its evolution. *Ultrasound Obstet Gynecol.* 2018 Mar;51(3):341-348.
82. Tachibana D, Glosemeyer P, Diehl W, Nakagawa K, Wada N, Kurihara Y, Fukui M, Koyama M, Hecher K. Time-interval analysis of ductus venosus flow velocity waveforms in twin-to-twin transfusion syndrome treated with laser surgery. *Ultrasound Obstet Gynecol.* 2015 May;45(5):544-50.
83. Maruotti GM, Saccone G, Ciardulli A, Mazzei LL, Berghella V, Martinelli P. Absent ductus venosus: case series from two tertiary centres. *J Matern Foetal Neonatal Med.* 2017 Jul 12:1-6.
84. Thomas JT, Petersen S, Cincotta R, Lee-Tannock A, Gardener G. Absent ductus venosus--outcomes and implications from a tertiary centre. *Prenat Diagn.* 2012 Jul;32(7):686-91.
85. Iliescu DG, Cara ML, Tudorache S, et al. Agenesis of ductus venosus in sequential first and second trimester screening. *Prenat Diagn.* 2014 Nov;34(11):1099-105.

86. Berg C, Kamil D, Geipel A, et al. Absence of ductus venosus-importance of umbilical venous drainage site. *Ultrasound Obstet Gynecol*. 2006 Sep;28(3):275-81.
87. Garcia-Delgado R, Garcia-Rodriguez R, Romero Requejo A, et al. Echographic features and perinatal outcomes in fetuses with congenital absence of ductus venosus. *Acta Obstet Gynecol Scand*. 2017 Oct;96(10):1205-1213.
88. Hofmann SR, Heilmann A, Häusler HJ, Kamin G, Nitzsche KI. Agenesis of the ductus venosus-A case with favorable outcome after early signs of cardiac failure. *J Clin Ultrasound*. 2013 Mar-Apr;41(3):187-90.
89. Jacob S, Farr G, De Vun D, Takiff H, Mason A. Hepatic manifestations of familial patent ductus venosus in adults. *Gut*. 1999 Sep;45(3):442-5.
90. Kamimatsuse A, Onitake Y, Kamei N, et al. Surgical intervention for patent ductus venosus. *Pediatr Surg Int*. 2010 Oct;26(10):1025-30.
91. Llanos D, Armijo J, Bodas A, Vaquero E, de la Pedraja I, Arrazola J. Transjugular closure of a patent ductus venosus in a symptomatic 14-year-old boy using a vascular plug. *J Pediatr*. 2014 Feb;164(2):426.e1-2.
92. Schierz IA, La Placa S, Giuffrè M, Montalbano G, Lenzo M, Corsello G. Transient hepatic nodular lesions associated with patent ductus venosus in preterm infants. *Am J Perinatol*. 2011 Mar;28(3):177-80.
93. Chacko A, Kock C, Joshi JA, Mitchell L, Ahmad S. Patent ductus venosus presenting with cholestatic jaundice in an infant with successful trans-catheter closure using a vascular plug device. *Indian J Radiol Imaging*. 2016 Jul-Sep;26(3):377-382.
94. Saito M, Seo Y, Yano Y, et al. Successful treatment using coil embolization of a symptomatic intrahepatic portosystemic venous shunt developing through a patent ductus venosus in a noncirrhotic adult. *Intern Med*. 2013;52(5):555-9.



95. Hara Y, Sato Y, Yamamoto S, et al. Successful laparoscopic division of a patent ductus venosus: report of a case. *Surg Today*. 2013 Apr;43(4):434-8.
96. Macchi V, Porzionato A, Tiengo C, Parenti A, De Caro R. Persistence of embryonic pattern of hepatocaval venous junction and patent ductus venosus in Budd-Chiari syndrome. *Clin Anat*. 2006 Oct;19(7):673-7.
97. Murayama K, Nagasaka H, Tate K, et al. Significant correlations between the flow volume of patent ductus venosus and early neonatal liver function: possible involvement of patent ductus venosus in postnatal liver function. *Arch Dis Child Fetal Neonatal Ed*. 2006 May;91(3):F175-9. Epub 2006 Jan 31.
98. Alomari AI, Chaudry G, Fox VL, Fishman SJ, Buchmiller TL. Atypical manifestation of patent ductus venosus in a child: intervening against a paradoxical presentation. *J Vasc Interv Radiol*. 2009 Apr;20(4):537-42.
99. Sharma R, Crowley J, Squires R, et al. Neonatal acute liver failure complicated by patent ductus venosus: diagnosis and management. *Liver Transpl*. 2013 Sep;19(9):1049-52.
100. Yamaguchi H, Kosugiyama K, Honda S, Tadao O, Taketomi A, Iwata S. Down Syndrome with Patent Ductus Venosus and Hepato-Biliary-Pancreatic Abnormalities. *Indian J Pediatr*. 2016 Jan;83(1):78-80.
101. Knisely AS. Patent ductus venosus and acute liver failure in the neonate: consider neonatal hemochromatosis with liver scarring. *Liver Transpl*. 2014 Jan;20(1):124.
102. Yoshimoto Y, Shimizu R, Saeki T, et al. Patent ductus venosus in children: a case report and review of the literature. *J Pediatr Surg*. 2004 Jan;39(1):E1-5.

103. Subramanian V, Kavassery MK, Sivasubramonian S, Sasidharan B. Percutaneous device closure of persistent ductus venosus presenting with hemoptysis. *Ann Pediatr Cardiol.* 2013 Jul-Dec; 6(2): 173–175.
104. Kamata S, Kitayama Y, Usui N, et al. Patent ductus venosus with a hypoplastic intrahepatic portal system presenting intrapulmonary shunt: a case treated with banding of the ductus venosus. *J Pediatr Surg.* 2000 Apr;35(4):655-7.
105. Aydinli M, Onal IK, Harmanci O, Ersoy O, Balkanci F, Bayraktar Y. A case of patent ductus venosus complicated with tumor-like lesions of the liver. *J Natl Med Assoc.* 2008 Jan;100(1):108-11.
106. Toib A, Goldstein SB, Khanna G, et al. Spontaneous echocardiographic contrast associated with portosystemic shunt due to persistent patent ductus venosus. *Congenit Heart Dis.* 2012 May Jun;7(3):E18-21.
107. Sagiv-Friedgut K, Witzling M, Dalal I, Vinkler C, Someh E, Levine A. Congenital patent ductus venosus: an association with the hyper IgE syndrome. *J Pediatr.* 2007 Feb;150(2):210 2.
108. Scheer I, Kivelitz D, Taupitz M, et al. Patent ductus venosus: diagnosis by MR angiography. *Pediatr Radiol.* 2001 Apr;31(4):279-82.